

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C12Q 1/68	A3	(11) International Publication Number: WO 99/57318 (43) International Publication Date: 11 November 1999 (11.11.99)
(21) International Application Number: PCT/US99/10251 (22) International Filing Date: 7 May 1999 (07.05.99) (30) Priority Data: 09/074,936 7 May 1998 (07.05.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/074,936 (CON) Filed on 7 May 1998 (07.05.98) (71) Applicant (for all designated States except US): SEQUENOM, INC. [US/US]; 11555 Sorrento Valley Road, San Diego, CA 92121 (US). (71)(72) Applicant and Inventor: HILLENKAMP, Franz [DE/DE]; Bahlmannstrasse 5, D-48147 Münster (DE). (72) Inventor; and (75) Inventor/Applicant (for US only): KÖSTER, Hubert [DE/US]; 8636-C Via Mallorca Drive, La Jolla, CA 92037 (US).		(74) Agent: SEIDMAN, Stephanie, L.; Heller Ehrman White & McAuliffe, Suite 700, 4250 Executive Square, La Jolla, CA 92037 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 23 March 2000 (23.03.00)
(54) Title: INFRARED MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRIC ANALYSIS OF MACROMOLECULES (57) Abstract Mixtures containing a biological macromolecule, such as a nucleic acid molecule or a polypeptide, and a liquid matrix, which absorbs infrared (IR) radiation, are provided. These mixtures are useful for analysis of the biological macromolecule by IR matrix assisted laser desorption/ionization (IR-MALDI) mass spectrometry. Also provided are processes for analyzing a biological macromolecule using IR-MALDI mass spectrometry. For example, processes for detecting the presence or identity of a biological macromolecule in a sample, or for sequencing a biological macromolecule are provided.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

Inter. Natl. Application No.

PCT/US 99/10251

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C1201/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERKENKAMP ET AL.: "PERFORMANCE OF INFRARED MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY WITH LASERS EMITTING IN THE 3 μ m WAVELENGTH RANGE" RAPID COMMUN MASS SPECTROM, vol. 11, 1997, pages 1399-1406, XP000870032	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
Y	the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 January 2000

Date of mailing of the international search report

04/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hagenmaier, S

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HILLENKAMP F ET AL: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF BIOPOLYMERS" ANALYTICAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. COLUMBUS, vol. 63, no. 24, page 1193-1203 XP000652496 ISSN: 0003-2700	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
Y	the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
X	--- SIEGEL ET AL.: "CALICHEAMICIN DERIVATIVES CONJUGATED TO MONOCLONAL ANTIBODIES: DETERMINATION OF LOADING VALUES AND DISTRIBUTIONS BY INFRARED AND UV MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY AND ELECTROSPRAY IONIZATION MASS SPECTROMETRY" ANAL. CHEM., vol. 69, 1997, pages 2716-2726, XP002128444 the whole document	130-134, 136, 150-152, 166,167, 169,170, 172
X	--- BERKENKAMP ET AL.: "ICE AS A MATRIX FOR IR-MATRIX ASSISTED LASER DESORPTION/IONIZATION: MASS SPECTRA FROM A PROTEIN SINGLE CRYSTAL" PNAS, vol. 93, 1996, pages 7003-7007, XP002128445 the whole document	130-134, 136, 150-152, 166,167, 169,170, 172
Y	--- WO 96 32504 A (UNIV BOSTON) 17 October 1996 (1996-10-17) See page 44, line 14- line 18 the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	--- WO 96 37630 A (STANFORD RES INST INT) 28 November 1996 (1996-11-28) the whole document --- -/--	92-129, 135, 137-149, 153-165, 168,171, 173-226

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 33000 A (GENETRACE SYSTEMS INC) 12 September 1997 (1997-09-12) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	WO 98 12355 A (GENETRACE SYSTEMS ;SHALER THOMAS A (US); TAN YUPING (US); BECKER C) 26 March 1998 (1998-03-26) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	WO 96 29431 A (SEQUENOM INC) 26 September 1996 (1996-09-26) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	WO 98 03684 A (HYBRIDON INC) 29 January 1998 (1998-01-29) the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
Y	HAHNER ET AL.: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY (MALDI) OF ENDONUCLEASE DIGESTS OF RNA" NUCLEIC ACIDS RESEARCH, vol. 25, no. 10, 1997, pages 1957-1964, XP002128446 the whole document ---	92-129, 135, 137-149, 153-165, 168,171, 173-226
A	WO 95 15001 A (WATERS CORP ;DORSCHER CRAIG A (US); JARRELL JOSEPH A (US); TOMANY) 1 June 1995 (1995-06-01) the whole document ---	
A	OVERBERG A ET AL: "MATRIXUNTERSTUETZTE LASERDESORPTIONS-MASSENSPEKTROMETRIE: EINE EMPFINDLICHE ANALYSETECHNIK FUER MAKROMOLEKUELE" LASER UND OPTOELEKTRONIK,DE,FACHVERLAG GMBH. STUTTGART, vol. 24, no. 1, 1992, pages 50-58, XP000247328 ISSN: 0722-9003 the whole document ---	

-/--

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>NORDHOFF ET AL.: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF NUCLEIC ACIDS WITH WAVELENGTHS IN THE ULTRAVIOLET AND INFRARED" RAPID COMMUN MASS SPECTROM, vol. 6, 1992, pages 771-776, XP000870028 the whole document</p> <p>---</p>	
A	<p>NELSON R W ET AL: "TIME-OF-FLIGHT MASS SPECTROMETRY OF NUCLEIC ACIDS BY LASER ABLATION AND IONIZATION FROM A FROZEN AQUEOUS MATRIX" RAPID COMMUNICATIONS IN MASS SPECTROMETRY,GB,LONDON, vol. 4, no. 9, 1990, page 348-351 XP002072976 the whole document</p> <p>---</p>	
A	<p>NORDHOFF E ET AL: "DIRECT MASS SPECTROMETRIC SEQUENCING OF LOW-PICOMOLE AMOUNTS OF OLIGODEOXYNUCLEOTIDES WITH UP TO 21 BASES BY MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY" JOURNAL OF MASS SPECTROMETRY,GB,WILEY, CHICHESTER, vol. 30, no. 1, 1995, page 99-112 XP002047878 ISSN: 1076-5174 the whole document</p> <p>---</p>	
A	<p>NORDHOFF ET AL.: "COMPARISON OF IR-AND UV-MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF OLIGODEOXYNUCLEOTIDES" NUCLEIC ACIDS RESEARCH, vol. 22, no. 13, 1994, pages 2460-2465, XP002128447 the whole document</p> <p>---</p>	
A	<p>NORDHOFF E: "Matrix-assisted laser desorption/ionization mass spectrometry as a new method for the characterization of nucleic acids" TRAC, TRENDS IN ANALYTICAL CHEMISTRY,GB,ANALYTICAL CHEMISTRY. CAMBRIDGE, vol. 15, no. 6, 1996, page 240-250 XP004034771 ISSN: 0165-9936 the whole document</p> <p>---</p>	

-/--

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/10251

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TANG K ET AL: "MATRIX-ASSISTED LASER DESORPTION/IONIZATION MASS SPECTROMETRY OF IMMOBILIZED DUPLEX DNA PROBES" NUCLEIC ACIDS RESEARCH,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 23, no. 16, 1995, page 3126-3131 XP002016562 ISSN: 0305-1048 the whole document	
P,Y	WO 98 20166 A (DEN BOOM DIRK VAN ;JURINKE CHRISTIAN (DE); HIGGINS G SCOTT (DE); L) 14 May 1998 (1998-05-14) the whole document	92-129, 135, 137-149, 153-165, 168,171, 173-226
P,X	BERKENKAMP ET AL.: "INFRARED MALDI MASS SPECTROMETRY OF LARGE NUCLEIC ACIDS" SCIENCE, vol. 281, July 1998 (1998-07), pages 260-262, XP002128448 the whole document	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
P,X	BERKENKAMP ET AL.: "INFRARED MALDI-MS OF LARGE NUCLEIC ACIDS" 46TH ASMS CONFERENCE ON MASS SPECTROMETRY AND ALLIED TOPICS, 21 May 1998 (1998-05-21), XP002128449 ORLANDO,USA the whole document	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172
P,X	KIRPEKAR ET AL.: "DOUBLE STRANDED DNA ANALYSED BY UV- AND IR-MALDI-MS" 46TH ASMS CONFERENCE ON MASS SPECTROMETRY AND ALLIED TOPICS, 21 May 1998 (1998-05-21), XP002128450 the whole document	1-91, 130-134, 136, 150-152, 166,167, 169,170, 172

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/10251

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9632504 A	17-10-1996	AU 5544696 A CA 2218188 A EP 0830460 A JP 11503611 T	30-10-1996 17-10-1996 25-03-1998 30-03-1999
WO 9637630 A	28-11-1996	US 5700642 A US 5830655 A AU 695705 B AU 5635296 A CA 2220418 A CN 1191575 A DE 69605669 D EP 0828855 A JP 11505127 T	23-12-1997 03-11-1998 20-08-1998 11-12-1996 28-11-1996 26-08-1998 20-01-2000 18-03-1998 18-05-1998
WO 9733000 A	12-09-1997	AU 2069597 A CA 2248084 A EP 0886681 A	22-09-1997 12-09-1997 30-12-1998
WO 9812355 A	26-03-1998	US 5965363 A AU 4591697 A	12-10-1999 14-04-1999
WO 9629431 A	26-09-1996	US 5605798 A AU 5365196 A CA 2214359 A CN 1202204 A EP 0815261 A JP 11508122 T	25-02-1997 08-10-1996 26-09-1996 16-12-1998 07-01-1998 21-07-1999
WO 9803684 A	29-01-1998	AU 4042597 A	10-02-1998
WO 9515001 A	01-06-1995	CA 2205040 A EP 0764264 A	01-06-1995 26-03-1997
WO 9820166 A	14-05-1998	US 5900481 A AU 5106998 A EP 0954612 A NO 992168 A AU 5247298 A DE 19782097 T EP 0937097 A NO 992167 A WO 9820019 A AU 5198098 A EP 0937096 A NO 992169 A WO 9820020 A	04-05-1999 29-05-1998 10-11-1999 06-07-1999 29-05-1998 14-10-1999 25-08-1999 05-07-1999 14-05-1998 29-05-1998 25-08-1999 06-07-1999 14-05-1998

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.